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Bone Marrow Necrosis in a Patient With Acute Myeloblastic Leukemia During Administration of G-CSF and Rapid Hematologic Recovery After Allotransplantation of Peripheral Blood Stem Cells

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Allogeneic peripheral blood stem cell transplantation from an HLA-identical sibling was performed for a 38-year-old male with refractory acute myeloblastic leukemia. The patient was conditioned with total body irradiation (TBI) and high-dose cytosine arabinoside (Ara-C). G-CSF (300 μg/body) was started for priming of residual leukemic cells 24 hrbefore the beginning of TBI (day −9). However, intolerable generalized bone pain appeared shortly after the start of first dose of G-CSF, and persisted for 3 days in spite of the cessation of G-CSF. Posttransplant hematopoietic engraftment was very rapid. Bone marrow biopsy specimens on day 14 and 30 showed typical bone marrow necrosis histologically. This is the first case of bone marrow necrosis during administration of G-CSF, and our experience suggests that PBSC could repopulate hematopoiesis in spite of severe bone marrow necrosis. Am. J. Hematol. 57:238–240, 1998.

Key words: bone marrow necrosis; conditioning therapy with G-CSF priming; allo-PBSCT; rapid hematologic recovery; repopulation of hematopoiesis

INTRODUCTION

Bone marrow necrosis is rarely diagnosed in patients antemortem and its presence signifies a poor prognosis [1,2]. The clinical management of patients with bone marrow necrosis is difficult. It usually develops in patients with malignancies [3–7], and the therapy for underlying disease sometimes relieves the patients with bone marrow necrosis. Ranaghan et al. discussed that the therapy could be improved by the use of both cytokines particularly aimed at promoting recovery of marrow stroma and chemotherapy regimens that are not highly toxic to bone marrow stroma and stems cells [8].

We described here a patient with acute myeloblastic leukemia who developed bone marrow necrosis during pretransplant conditioning therapy for allogeneic peripheral blood stem cell transplantation (allo-PBSCT), but obtained rapid engraftment posttransplant.

CASE REPORT

A 38-year-old male with acute myeloblastic leukemia (FAB M5b) achieved complete remission (CR) after conventional remission induction chemotherapy in October 1994. Four months later, however, leukemia relapsed and reinduction of CR failed. Then, allo-PBSCT from his HLA-identical brother was planned. Before the pretransplant conditioning therapy, a white blood cell (WBC) count was 32.5×10^9/L consisting of 87% blasts, a hemoglobin (Hb) concentration 9.9 g/dL, and a platelet (PLT) count 20.0×10^9/L. A bone marrow aspirate showed leukemic proliferation with 87% leukemic cells in differentials of nucleated cells (95.0×10^9/L). Since leukemic cells from this patient responded vigorously to

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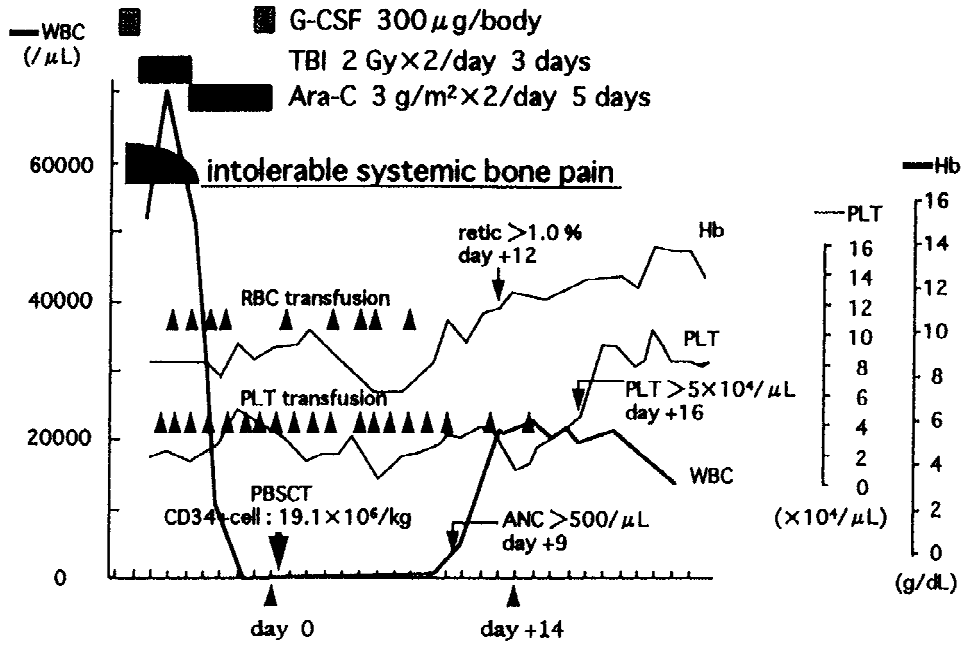

Fig. 1. The clinical course of the patient in early phase of transplantation.

G-CSF stimulation when evaluated by in vitro ^{3}H-thymidine uptake, we employed the G-CSF-combined conditioning regimen [9]. G-CSF was intended to be administered from 24 hr before the beginning of total body irradiation (TBI) through the end of cytosine arabinoside (Ara-C) therapy and was started on day-9 at a dose of 300 μg/body by drip infusion for 1 hr. Half an hour later after the first dose of G-CSF, however, the patient complained of very severe generalized bone pain that could not be controlled even by narcotics. WBC counts were increased from 32.5 × 10^9/L (blasts 87%) to 52.1 × 10^9/L (blasts 82%) 3 hr later after the end of the first G-CSF dose. The bone pain lasted for 3 days in spite of the cessation of G-CSF. Specific findings for disseminated intravascular coagulation (DIC) were not observed. The pretransplant conditioning regimen consisted of TBI (12 Gy in 6 fractions on days -8 through -6) and Ara-C (24 g/m^2, in 8 divided doses every 12 hr on days -5 through -2), and the patient was infused with 19.1 × 10^6 CD34 + cells/kg, which were mobilized by G-CSF and collected by apheresis from the sibling donor [10]. Cyclosporin A and methylprednisolone were given for GVHD prophylaxis. Hematopietic engraftment was very rapid; days of an absolute neutrophil count (ANC) > 0.5 × 10^9/L, a reticulocyte count > 1.0%, a PLT count > 50.0 × 10^9/L were 9, 12, and 16, respectively. Allogeneic engraftment was confirmed by variable number of tandem repeats (VNTR) analysis. The clinical course in an early phase of transplantation is illustrated in Figure 1. The bone marrow aspiration resulted in dry tap on day 14 and the biopsy specimen from the left posterior iliac crest showed the necrosis of bone marrow and trabeculae with partial normal hemopoiesis (Fig. 2), and similar findings from the right posterior iliac crest were obtained on day 30. Acute GVHD did not develop. The hematopoietic reconstitution was maintained until the disease recurred on day 42 when leukemic cells emerged in the peripheral blood. Bone marrow scintillation scans using ^{111}In on day 50 showed low uptakes within the bone marrow, especially in the iliac bone, with increased uptakes in the femoral bone instead. High uptakes were also observed in the spleen and the liver. Leukoerythroblastosis detected on day 7 persisted in peripheral blood until he died of progression of the disease on day 70. At autopsy, bone marrow in the vertebra was found to be grayish-brown in color, and diffuse infiltration of leukemic cells with only few hematopoietic islands was revealed microscopically. No lesion of bone marrow necrosis was observed. A few erythroblasts were observed in the spleen and the liver, which were confirmed by immunohistochemical staining for glycophorin A.

DISCUSSION

Intolerable generalized bone pain is a typical feature of bone marrow necrosis [1]. In addition, histological findings of the bone marrow biopsy specimens and radiological findings from bone marrow scintigram indicated the presence of systemic bone marrow necrosis [2]. The necrosis of bone trabeculae is not usually observed in bone marrow necrosis [2], suggesting that the marrow necrosis in this case may be extremely severe. Bone marrow necrosis is sometimes associated with DIC [11], but

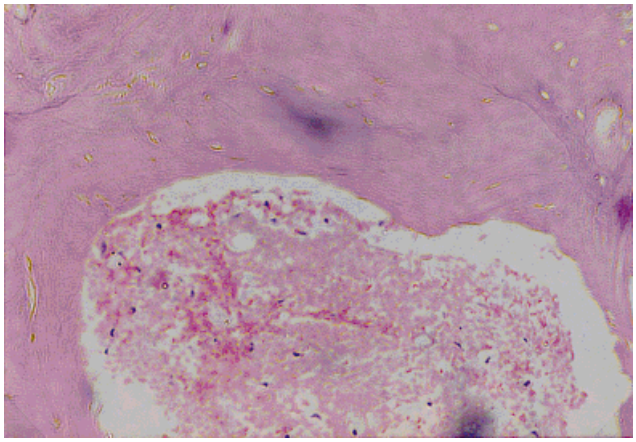

Fig. 2. Bone marrow biopsy on day 14 (H & E, ×100). Bone marrow are diffusely eosinophilic, amorphous, and devoid of fat or stroma. Lacunae of many bone trabeculae lack osteocytes.

it was not found in our case. Because the bone pain emerged immediately after the administration of G-CSF, rapid expansion of leukemic cells and microcirculation failure of the bone marrow induced by G-CSF may be factors in the pathogenesis of the bone marrow necrosis [12].

Successful treatment for severe marrow dysfunction has been reported, for instance, allogeneic bone marrow transplantation for severe myelofibrosis [13–16]. Damaged marrow can be replaced by normal hemopoietic foci in this setting. Engraftment was very rapid in our case despite the development of bone marrow necrosis. This may be facilitated by the infusion of a rather high number of PBSC. However, it has not been proven whether transplanted PBSC could engraft to remain normal marrow or necrotic marrow.

High uptakes of ^{111}In and the presence of erythroblasts in the liver and the spleen in addition to the leukoerythroblastosis indicated that some extramedullary hemopoiesis existed in the liver and the spleen, where the transplanted hematopoietic cells can lodge and colonize [17]. But it is not clear whether extramedullary hemopoiesis is exceptional in the case of transplantation for bone marrow necrosis, because it was not evaluated prior to the relapse of leukemia in our case.

In conclusion, this is the first case of bone marrow necrosis during administration of G-CSF, and PBSC could repopulate hematopoiesis in the presence of severe marrow necrosis.

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